Characterizing risks from dioxin and related compounds requires the integration of complex data sets and the use of science-based inferences regarding hazard, mode of action, dose response, and exposure. It also requires consideration of incremental exposures in the context of an existing background exposure that is, for the most part, independent of local sources and dominated by exposure through the food supply. Finally, this characterization must consider risks to special populations and developmental stages (subsistence fishers, children, etc.) as well as the general population. It is important that this characterization convey the current understanding of the scientific community regarding these issues, highlight uncertainties in this understanding, and specify where assumptions or inferences have been used in the absence of data. Although characterization of risk is inherently a scientific exercise, by its nature it must go beyond empirical observations and draw conclusions in untested areas. In some cases, these conclusions are, in fact, untestable given the current capabilities in analytical chemistry, toxicology, and epidemiology. This situation should not detract from our confidence in a well structured and documented characterization of risk, but should serve to confirm the importance of considering risk assessment as an iterative process that benefits from evolving methods and data collection.

Dioxin and related compounds can produce a wide variety of effects in animals and might produce many of the same effects in humans.

There is adequate evidence based on all available information discussed in Parts I and II of this reassessment, as well as that discussed in this Integrated Summary, to support the inference that humans are likely to respond with a broad spectrum of effects from exposure to dioxin and

related compounds. These effects will likely range from biochemical changes at or near background levels of exposure to adverse effects with increasing severity as body burdens increase above background levels. Enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals represent effects of unknown clinical significance but that may be early indicators of toxic response. Induction of activating/metabolizing enzymes at or near background levels, for instance, may be adaptive, and in some cases, beneficial, or may be considered adverse. Induction may lead to more rapid metabolism and elimination of potentially toxic compounds, or may lead to increases in reactive intermediates and may potentiate toxic effects. Demonstration of examples of both of these situations is available in the published literature and events of this type formed the basis for a biologically based model discussed in Section 5. Subtle effects, such as the impacts on neurobehavioral outcomes, thyroid function, and liver enzymes (AST and ALT) seen in the Dutch children exposed to background levels of dioxin and related compounds, or changes in circulating reproductive hormones in men exposed to TCDD, illustrate the types of responses that support the finding of arguably adverse effects at or near background body burdens. Clearly adverse effects including, perhaps, cancer may not be detectable until exposures contribute to body burdens that exceed background by one or two orders of magnitude (10 or 100 times). The mechanistic relationships of biochemical and cellular changes seen at or near background body burden levels to production of adverse effects detectible at higher levels remains uncertain, but data are accumulating to suggest mode of action hypotheses for further testing.

It is well known that individual species vary in their sensitivity to any particular dioxin effect. However, the evidence available to date indicates that humans most likely fall in the middle of the range of sensitivity for individual effects among animals rather than at either extreme. In other words, evaluation of the available data suggests that humans, in general, are neither extremely sensitive nor insensitive to the individual effects of dioxin-like compounds. Human data provide direct or indirect support for evaluation of likely effect levels for several of the endpoints discussed in the reassessment, although the influence of variability among humans remains difficult to assess. Discussions have highlighted certain prominent, biologically significant effects of TCDD and related compounds. In TCDD-exposed men, subtle changes in biochemistry and physiology such as enzyme induction, altered levels of circulating reproductive hormones, or reduced glucose tolerance and, perhaps, diabetes, have been detected in a limited number of epidemiologic studies. These findings, coupled with knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism, and developmental and/or reproductive biology, and, perhaps, other effects in the range of current human exposures. These biochemical, cellular, and organ-level endpoints have been shown to be affected by TCDD, but specific data on these endpoints do not generally exist for other congeners. Despite this lack of

congener-specific data, there is reason to infer that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence.

In this volume, dioxin and related compounds are characterized as carcinogenic, developmental, reproductive, immunological, and endocrinological hazards. The deduction that humans are likely to respond with noncancer effects from exposure to dioxin-like compounds is based on the fundamental level at that these compounds impact cellular regulation and the broad range of species that have proven to respond with adverse effects. For example, because developmental toxicity following exposure to TCDD-like congeners occurs in fish, birds, and mammals, it is likely to occur at some level in humans. It is not currently possible to state exactly how or at what levels individuals will respond with specific adverse impacts on development or reproductive function, but analysis of the Dutch cohort data and laboratory animal studies suggests that some effects may occur at or near background levels. Fortunately, there have been few human cohorts identified with TCDD exposures high enough to raise body burdens significantly over background levels (see Table 5-1 and Figure 5-1 in Section 5), and when these cohorts have been examined, relatively few clinically significant effects were detected. The lack of exposure gradients and adequate human information and the focus of most currently available epidemiologic studies on occupationally TCDD-exposed adult males makes evaluation of the inference that noncancer effects associated with exposure to dioxin-like compounds may be occurring, difficult. It is important to note, however, that when exposures to very high levels of dioxin-like compounds have been studied, such as in the Yusho and Yu- Cheng cohorts, a spectrum of adverse effects have been detected in men, women, and children. Some have argued that to deduce that a spectrum of noncancer effects will occur in humans in the absence of better human data overstates the science; most scientists involved in the reassessment as authors and reviewers have indicated that such inference is reasonable given the weight-of-the-evidence from available data. As presented, this logical conclusion represents a testable hypothesis which may be evaluated by further data collection. EPA, its Federal colleagues, and others in the general scientific community are continuing to fill critical data gaps that will reduce our uncertainty regarding both hazard and risk characterization for dioxin and related compounds.

Dioxin and related compounds are structurally related and elicit their effects through a common mode of action.

The scientific community has identified and described a series of common biological steps that are necessary for most, if not all, of the observed effects of dioxin and related compounds in vertebrates including humans. Binding of dioxin-like compounds to a cellular protein called the AhR represents the first step in a series of events attributable to exposure to dioxin-like compounds including biochemical, cellular, and tissue-level changes in normal biological

processes. Binding to the AhR appears to be necessary for all well-studied effects of dioxin but is not sufficient, in and of itself, to elicit these responses. There remains some uncertainty as to whether every dioxin response is AhR-mediated. Sensitive biological tools such as aryl hydrocarbon receptor deficient ($AhR^{-/-}$) mice indicate a small residual of effects to exposure to TCDD that does not allow us to rule out receptor-independent alternative pathways. The well-documented effects elicited by exposure of animals and, in some cases, humans, to 2,3,7,8-TCDD are shared by other chemicals with similar structure and AhR binding characteristics. In the past 5 years, significant data has accumulated that support the concept of toxicity equivalence, that is at the heart of risk assessment for the complex mixtures of dioxin and related compounds encountered in the environment. These data have been analyzed and summarized in Part II, Chapter 9. This chapter has been added to EPA's dioxin reassessment to address questions raised by the Agency's Science Advisory Board (SAB) in 1995. The SAB suggested that, because the TEQ approach was a critical component of risk assessment for dioxin and related compounds, the Agency should be explicit in its description of the history and application of the process and go beyond reliance on the Agency's published reference documents on the subject (U.S. EPA, 1987, 1989).

EPA and the international scientific community have adopted toxicty equivalence of dioxin and related compounds as prudent science policy.

Dioxin and related compounds always exist in nature as complex mixtures. As discussed in the Exposure Document, these complex mixtures can be characterized through analytic methods to determine concentrations of individual congeners. Dioxin and related compounds can be quantified and biological activity of the mixture can be estimated using relative potency values and an assumption of dose additivity. Such an approach has evolved over time to form the basis for the use of TEQ in risk assessment for this group of compounds. Although such an approach is dependent on critical assumptions and scientific judgement, it has been characterized as a "useful, interim" way to deal with the complex mixture problem and has been accepted by numerous countries and several international organizations. Alternative approaches, including the assumption that all congeners carry the toxicity equivalence of 2,3,7,8-TCDD, or that all congeners other than 2,3,7,8-TCDD can be ignored, have been generally rejected as inadequate for risk assessment purposes.

Significant additional literature is now available on the subject of toxicity equivalence of dioxin and related compounds, and Chapter 9 provides the reader with a summary that is up to date through 1999. A recent international evaluation of all of the available data (van den Berg et al., 1998) has reaffirmed the TEQ approach and has provided the scientific community with the latest values for TEFs for PCDDs, PCDFs, and dioxin-like PCBs. Consequently, we can infer with

greater confidence that humans will respond to the cumulative exposure of AhR-mediated chemicals. The position taken in this reassessment is that these 1998 TEFs should be adopted for use by the Agency. Future research will be needed to address remaining uncertainties inherent in the current approach. The WHO has suggested that the TEQ scheme be reevaluated on a periodic basis and that TEFs and their application to risk assessment be reanalyzed to account for emerging scientific information.

Complex mixtures of dioxin and related compounds are highly potent, "likely" carcinogens.

With regard to carcinogenicity, a weight-of-the-evidence evaluation suggests that mixtures of dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs) are strong cancer promoters and weak direct or indirect initiators and likely to present a cancer hazard to humans. Because dioxin and related compounds always occur in the environment and in humans as complex mixtures of individual congeners, it is appropriate that the characterization apply to the mixture. According to the Agency's revised draft Cancer Guidelines, the descriptor likely is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans. Adequate data are recognized to span a wide range. The data for complex mixtures of dioxin and related compounds represents a case that, according to the draft Guidelines, would approach the strong-evidence end of the adequate-data spectrum. Epidemiologic observations of an association between exposure and cancer responses (TCDD); unequivocal positive responses in both sexes, multiple species, and different routes in lifetime bioassays or initiation-promotion protocols or other shorter-term in vivo systems such as transgenic models (TCDD plus numerous PCDDs, PCDFs, dioxin-like PCBs); and mechanistic or mode-of action data that are assumed to be relevant to human carcinogenicity (PCDDs, PCDFs, dioxin-like PCBs) all support the description of complex mixtures of dioxin and related compounds as likely human carcinogens.

Even though the database from cancer epidemiologic studies remains controversial, it is the view of this reassessment that this body of evidence is supported by the laboratory data indicating that TCDD probably increases cancer mortality of several types. Although not all confounders were ruled out in any one study, positive associations between surrogates of dioxin exposure, either length of occupational exposure or proximity to a known source combined with some information based on measured blood levels, and cancer have been reported. These data suggest a role for dioxin exposure to contribute to a carcinogenic response but do not confirm a causal relationship between exposure to dioxin and increased cancer incidence. Available human studies alone cannot demonstrate whether a cause-and-effect relationship between dioxin exposure and increased incidence of cancer exists. Therefore, evaluation of cancer hazard in humans must include an evaluation of all of the available animal and in vitro data as well as the data from exposed human populations.

As discussed earlier in Section 2.2.1.4, under EPA's current approach, individual congeners can also be characterized as to their carcinogenic hazard. TCDD is best characterized as "carcinogenic to humans." This means that, based on the weight of all of the evidence (human, animal, mode of action), TCDD meets the criteria that allows U.S. EPA and the scientific community to accept a causal relationship between TCDD exposure and cancer hazard. The guidance suggests that "carcinogenic to humans" is an appropriate descriptor of human carcinogenic potential when there is an absence of conclusive epidemiologic evidence to clearly establish a cause-and-effect relationship between human exposure and cancer, but there is compelling carcinogenicity in animals and mechanistic information in animals and humans demonstrating similar modes of carcinogenic action. The "carcinogenic to humans" descriptor is suggested for TCDD because all of the following conditions are met:

- There is evidence from occupational epidemiologic studies for an association between TCDD exposure and increases in cancer at all sites, in lung cancer and, perhaps, at other sites, but the data are insufficient on their own to demonstrate a causal association.
- There is extensive carcinogenicity in both sexes of multiple species at multiple sites.
- There is general agreement that the mode of TCDD's carcinogenicity is AhR dependent and proceeds through modification of the action of a number of receptor and hormone systems involved in cell growth and differentiation, such as the epidermal growth factor receptor and estrogen receptor.
- Key events such as equivalent body burdens in animals and in human populations expressing an association between exposure to TCDD and cancer, and the determination of active AhR and dioxin responsive elements in the general human population. There is no reason to believe that these events would not occur in the occupational cohorts studied.

Other individual dioxin-like compounds are characterized as "likely" human carcinogens primarily because of the lack of epidemiological evidence associated with their carcinogenicity, although the inference based on toxicity equivalence is strong that they would behave in humans as TCDD does. Other factors, such as the lack of congener-specific chronic bioassays, also support this characterization. For each congener, the degree of certainty is dependent on the available congener-specific data and their consistency with the generalized mode of action that underpins toxicity equivalence for TCDD and related compounds. On the basis of this logic, complex environmental mixtures of TCDD and dioxin-like compounds should be characterized as "likely" carcinogens, with the degree of certainty of the characterization being dependent on the constituents of the mixture, when known. For instance, the hazard potential, although "likely," would be characterized differently for a mixture whose TEQ was dominated by OCDD as compared with one which was dominated by pentaCDF.

Although uncertainties remain regarding quantitative estimates of upper bound cancer risk from dioxin and related compounds, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in evaluation of the slope of the dose-response curve at the low end of the observed range (using the LED_{01}) using a simple proportional (linear) model and a calculation of both upper bound risk and margin of exposure (MOE) based on human equivalent background exposures and associated body burdens. Evaluation of shape parameters (used to estimate degree of linearity or nonlinearity of dose-response within the range of observation) for biochemical effects indicates that many of these biochemical effects can be hypothesized to be to key events in a generalized dioxin mode-of action model. These analyses do not argue for significant departures from linearity below a calculated ED_{01} for endpoints potentially related to cancer response, for at least one to two orders of magnitude lower exposure.

Risk estimates for intakes associated with background body burdens or incremental exposures based on this slope factor represent a plausible upper bound on risk based on the evaluation of animal and human data. The slope factors based on the most sensitive cancer responses, both animal and human, calculated in Section 5 fall in a range of 5×10^{-3} to 5×10^{-4} per pg TEQ/kgBW/day. The ranges of estimates of upper bound cancer potency calculated from the human and animal data analyzed in Part II, Chapter 8, overlap. The range above is bounded on the upper end by the estimate of slope from the Hamburg cohort epidemiology study and on the lower end by the estimate from the reanalyzed Kociba study. Consequently, the Agency, although fully recognizing this range and the public health conservative nature of the slope factors that make up the range, suggests the use of 5×10^{-3} per pg TEQ/kgBW/day as an estimator of upper bound cancer risk for both background intakes and incremental intakes above background. Slope factors allow the calculation of the probability of cancer risk for the highly vulnerable in the population (estimated to be the top 5% or greater). Although there may be individuals in the population who might experience a higher cancer risk on the basis of genetic factors or other determinants of cancer risk not accounted for in epidemiologic data or animal studies, the vast majority of the population is expected to have less risk per unit of exposure and some may have zero risk. Based on these slope factor estimates (per pg TEQ/kgBW/day), average current background body burdens (5 ng/kgBW) resulting from average intakes of approximately 3 pgTEQ/kgBW/day are in the range of 10^{-3} to 10^{-2}. A very small percentage of the population (< 1%) may experience risk that are 2-3 times higher than this if they are among both the most vulnerable and the most highly exposed (among the top 5%) based on dietary intake of dioxin and related compounds. This range of upper bound risk for the general population has increased an order of magnitude from the risk described at background exposure levels based on EPA's draft of this reassessment (10^{-4}-10^{-3}) (U.S. EPA, 1994).

Despite the use of the epidemiology data to describe an upper bound on cancer risk, the Peer Panel that met in September 1993 to review an earlier draft of the cancer epidemiology

chapter suggested that the epidemiology data alone were still not adequate to implicate dioxin and related compounds as "known" human carcinogens, but that the results from the human studies were largely consistent with observations from laboratory studies of dioxin-induced cancer and, therefore, should not be dismissed or ignored. Other scientists, including those who attended the Peer Panel meeting, felt either more or less strongly about the weight of the evidence from cancer epidemiology studies, representing the range of opinion that still exists on the interpretation of these studies. Similar opinions were expressed in the comments documented in the SAB's report in 1995 (U.S. EPA,1995). More recently, the International Agency for Research on Cancer (1997), in its reevaluation of the cancer hazard of dioxin and related compounds, found that whereas the epidemiologic database for 2,3,7,8-TCDD was still "limited," the overall weight of the evidence was sufficient to characterize 2,3,7,8-TCDD as a Category 1 "known" human carcinogen. Other related members of the class of dioxin-like compounds were considered to have "inadequate" epidemiologic data to factor into hazard categorization. A similar classification has been proposed within the context of the Department of Health and Human Services' Report on Carcinogens (NTP, 2000). They too base their characterization on the broad base of human, animal, and mode-of-action information in humans and animals that supports this conclusion. Therefore, given that 2,3,7,8-TCDD is contained in complex mixtures of dioxin and related compounds, and that the TEQ approach has been adopted as a reasonable approach to assessing risks of these complex mixtures, it is also reasonable to apply estimates of upper bound cancer potency derived from epidemiology studies where 2,3,7,8-TCDD was associated with excess cancer risk to complex mixtures of dioxin and related compounds.

The current evidence suggests that both receptor binding and most early biochemical events such as enzyme induction are likely to demonstrate low-dose linearity. The mechanistic relationship of these early events to the complex process of carcinogenesis remains to be established. If these findings imply low-dose linearity in biologically based cancer models under development, then the probability of cancer risk will be linearly related to exposure to TCDD at low doses. Until the mechanistic relationship between early cellular responses and the parameters in biologically based cancer models is better understood, the shape of the dose-response curve for cancer in the below the range of observation can only be inferred with uncertainty. Associations between exposure to dioxin and certain types of cancer have been noted in occupational cohorts with average body burdens of TCDD approximately 1- 3 orders of magnitude (10-1,000 times) higher than average TCDD body burdens in the general population. The average body burden in these occupational cohorts level is within 1-2 orders of magnitude (10-100 times) of average background body burdens in the general population in terms of TEQ (see Table 5-1 and Figure 5-1). Thus, there is no need for large-scale low-dose extrapolations in order to evaluate background intakes and body burdens, and little if any data to suggest large departures from linearity in this somewhat narrow window between the lower end of the range of observation and

the range of general-population background exposures. Nonetheless, the relationship of apparent increases in cancer mortality in these worker populations to calculations of general population risk remains a source of uncertainty.

TCDD has been clearly shown to increase malignant tumor incidence in laboratory animals. In addition, a number of studies analyzed in this reassessment demonstrate other biological effects of dioxin related to the process of carcinogenesis. Initial attempts to construct a biologically based model for certain dioxin effects as described in this reassessment will need to be continued and expanded to accommodate more of the available biology and to apply to a broader range of potential health effects associated with exposure to dioxin-like compounds.

Use a "margin-of-exposure approach" to evaluate risk for noncancer and cancer endpoints.

The likelihood that noncancer effects may be occurring in the human population at environmental exposure levels is often evaluated using a MOE approach. The Agency has used this approach for a number of years in its assessment of the safety of pesticides. This concept has also been incorporated into the revised Cancer Risk Assessment guidelines. A MOE is calculated by dividing a "point of departure" for extrapolation purposes at the low end of the range of observation in human or animal studies (the human-equivalent animal LOAEL, NOAEL, BMD, or effective dose [EDxx]) by the human exposure or body burden level of interest. Generally speaking, when considering either background exposures or incremental exposures plus background, MOEs in range of 100-1,000 are considered adequate to rule out the likelihood of significant effects occurring in humans based on sensitive animal responses or results from epidemiologic studies. The adequacy of the MOE to be protective of health must take into account the nature of the effect at the "point of departure," the slope of the dose-response curve, the adequacy of the overall database, interindividual variability in the human population, and other factors. Considering MOEs based on incremental exposures alone divided by the human exposure of interest, is not considered to give an accurate portrayal of the implications of that exposure unless background exposures are insignificant.

One of the difficulties in assessing the potential health risk of dioxins is that background exposures not be insignificant when based on total TEQ. The average levels of background intake and associated body burdens of dioxin-like compounds in terms of TEQs in the general population would be well within a factor of 100 of human-equivalent exposure levels associated with NOELS, LOAELs, BMDs, or ED_{01} values in laboratory animals exposed to TCDD or TCDD equivalents. In many cases, the MOE compared to background using these endpoints is a factor of 10 or less (see Tables 2-2 and 2-3). These estimates, although variable, suggest that any choice of body burden, as a point of departure, above 100 ng/kg would likely yield >1% excess risk for some endpoint in humans (see Section II, Chapter 8). Also, choosing of a point of departure below 1 ng/kg would likely be an extrapolation below the range of these data and would likely

represent a risk of < 1%. Any choice for a point of departure in the middle range of 1 ng/kg to 100 ng/kg would be supported by the analyses, although the data provide the greatest support for a point of departure in the range of 10 ng/kg to 50 ng/kg.

Because of the relatively high background compared to effect levels, the Agency is not recommending the derivation of an RfD for dioxin and related compounds. Although RfDs are often useful because they represent a health risk goal below which there is likely to be no appreciable risk of noncancer effects over a lifetime of exposure, their primary use is to evaluate increments of exposure from specific sources when background exposures are low and insignificant. Any RfD that the Agency would recommend under the traditional approach for setting an RfD is likely to be 2-3 orders of magnitude (100-1,000) below current background intakes and body burdens. Because exceeding the RfD is not a statement of risk, discussion of an RfD for an incremental exposure when the RfD has already been exceeded by average background exposures is meaningless.

When evaluating incremental exposures associated with specific sources, knowing the increment relative to background may help to understand the impact of the incremental exposure. For instance, it would be misleading to suggest that an incremental exposure of 0.001 pg TEQ/kg/day was below the RfD if "background" exposures were already at or above that level. On the other hand, as part of the total, the increment represents less than a 0.1% increase over average "background," and we estimate that individuals within the 50%-95% range of exposure within the population may be 2-3 times (200%-300%) higher. This has led us to suggest that perhaps the best information for a decision-maker to have is: (1) a characterization of average "background" exposures; (2) a characterization of the percent increase over background of individuals or subpopulations of interest; and (3) a policy statement about when increases over average "background" become significant for the decision. This is not easy because one could argue that, given high "background," any addition, if it is widespread, is too much. On the other hand, someone else could argue that a 10% increase in incremental exposure for a small population around a specific point source would be well within the general population exposures and would not constitute a disproportionate exposure or risk. In this case, the strategy might be to bring average "background" exposures down and to focus on large incremental exposures or highly susceptible populations. This would be a strategy that would parallel the Agency's lead strategy. Other parallel issues between dioxin-like compounds and lead are under discussion within the Agency.

ATSDR (1999) set a minimal risk level (MRL), which is defined similarly to the EPA's RfD, for dioxin and related compounds of 1.0 pg TEQ/kgBW/day. Some of the data regarding lower bounds on the ED_{01}s from various noncancer effects call that MRL into question. WHO (2000) has set a tolerable daily intake of 1-4 pg TEQ/kgBW/day and has indicated that, although current exposures in that range are "tolerable" (a risk management decision rather than a risk

assessment), efforts should be made to ultimately reduce intake levels. Findings in this reassessment appear to be supportive of that recommendation.

Children's risk from exposure to dioxin and related compounds may be increased, but more data are needed to fully address this issue.

The issue of children's risk from exposure to dioxin-like compounds has been addressed in a number of sections throughout this reassessment. Data suggest a sensitivity of response in both humans and animals during the developmental period, both prenatally and postnatally. However, data are limited. Because evaluation of the impacts of early exposures on both children's health and health later in life is important to a complete characterization of risk, collection of additional data in this area should be a high priority to reduce uncertainties in future risk assessments.

Data from the Dutch cohort of children exposed to PCBs and dioxin-like compounds suggest impacts of exposure to background levels of dioxin and related compounds prenatally and, perhaps, postnatally on neurobehavioral outcomes, thyroid function, and liver enzymes (AST and ALT). Although these effects cannot be attributed solely to dioxin and related compounds, several associations suggest that these are, in fact, likely to be Ah-mediated effects. An investigation of background dioxin exposure and tooth development was done in Finnish children as a result of studies of dental effects in dioxin-exposed rats, mice, and nonhuman primates, and in PCB-exposed children. The Finnish investigators examined enamel hypomineralization of permanent first molars in 6-7 year old children. The length of time that infants breast fed was not significantly associated with either mineralization changes or with TEQ levels in the breast milk. However, when the levels and length of breast feeding were combined in an overall score, a statistically significant association was observed ($r = 0.3$, $p = 0.003$, regression analysis).

In addition, effects have been seen where significantly elevated exposure occurred. The incidents at Yusho and Yu-Cheng resulted in increased perinatal mortality and low birthweight in infants born to women who had been exposed. Rocker bottom heal was observed in Yusho infants, and functional abnormalities have been reported in Yu-Cheng children. The similarity of effects observed in human infants prenatally exposed to the complex mixture in Yusho and Yu-Cheng with those reported in adult monkeys exposed only to TCDD suggests that at least some of the effects on children are due to the TCDD-like congeners in the contaminated rice oil ingested by the mothers of these children. The similar responses include a clustering of effects in organs derived from the ectodermal germ layer, referred to as ectodermal dysplasia, including effects on the skin, nails, and Meibomian glands; and developmental and psychomotor delay during developmental and cognitive tests. Some investigators believe that because all of these effects in the Yusho and Yu-Cheng cohorts do not correlate with TEQ, some of the effects are exclusively due to nondioxin-like PCBs or a combination of all the congeners. In addition, on the basis of these data, it is still not clear to what extent there is an association between overt

maternal toxicity and embryo/fetal toxicity in humans. Further studies in the offspring as well as follow-up to the Seveso incident may shed further light on this issue. In addition to chloracne and acute responses to TCDD exposure seen in Seveso children, elevated levels of serum GGT have been observed within a year after exposure in some of the more highly exposed Seveso children. Long-term pathologic consequences of elevated GGT have not been illustrated by excess mortality from liver disorders or cancer or in excess morbidity, but further follow-up is needed. It must be recognized that the absence of an effect thus far does not obviate the possibility that the enzyme levels may have increased concurrent to the exposure but declined after cessation. The apparently transient elevations in ALT levels among the Seveso children suggest that hepatic enzyme levels other than GGT may react in this manner to 2,3,7,8-TCDD exposure.

Impacts on thyroid hormones provide an example of an effect of elevated postnatal exposure to dioxin and related compounds. Several studies of nursing infants suggest that ingestion of breast milk with a higher dioxin TEQ may alter thyroid function. Thyroid hormones play important roles in the developing nervous system of all vertebrate species, including humans. In fact, thyroid hormones are considered so important in development that in the United States all infants are tested for hypothyroidism shortly after birth. Results from the studies mentioned above suggest a possible shift in the population distribution of thyroid hormone levels, particularly T4, and point out the need for collection of longitudinal data to assess the potential for long-term effects associated with developmental exposures. The exact processes accounting for these observations in humans are unknown, but when put in perspective of animal responses, the following might apply: dioxin increases the metabolism and excretion of thyroid hormone, mainly T4, in the liver. Reduced T4 levels stimulate the pituitary to secrete more TSH, which enhances thyroid hormone production. Early in the disruption process, the body can overcompensate for the loss of T4, which may result in a small excess of circulating T4 in response to the increased TSH. In animals, given higher doses of dioxin, the body is unable to maintain homeostasis, and TSH levels remain elevated and T4 levels decrease.

A large number of studies in animals have addressed the question of effects of dioxin-like chemicals after in utero or lactational exposure. These have included both single-congener studies and exposures to complex mixtures. However, the vast majority of the data are derived from studies of 2,3,7,8-TCDD, or single congeners (e.g., PCB 77) or commercial mixtures of PCBs. Exposure patterns have included single doses to the dams as well as dosing on multiple days during gestation beginning as early as the first day of gestation. These studies are discussed in detail in Part II, Chapter 5. The observed toxic effects include developmental toxicity, neurobehavioral and neurochemical alterations, endocrine effects, and developmental immunotoxicity. For instance, results of this body of work suggest that 2,3,7,8-TCDD clearly has the potential to produce alterations in male reproductive function (rats and hamsters) and male sexual behavior (rats) after prenatal exposure. In addition, impacts on neuromotor and cognitive

behavior as well as development of the immune system have been indicated in a number of studies.

No epidemiological data and limited animal data are available to address the question of the potential impact of exposure to dioxin-like compounds on childhood cancers or on cancers of later life. Given the relative impact of nursing on body burdens (see the discussion of breast milk exposures and body burdens below), direct impacts of increased early postnatal exposure on the carcinogenic process are expected to be small. This conclusion is based on the reasonable assumptions that cancer risk is a function of average lifetime body burden or that, because dioxin is a potent cancer promoter rather than a direct initiator of the cancer process, exposures later in life might be more important than those received earlier. However, recent studies of Brown et al. (1998) suggest that prenatal exposure of rats to dioxin and related compounds may indirectly enhance their sensitivity as adults to chemical carcinogenesis from other chemical carcinogens. Further work is needed to evaluate this issue.

In addition to potential vulnerability during development, fetuses, infants, and children are exposed to dioxins through several routes. The fetus is exposed in utero to levels of dioxin and related compounds that reflect the body burden of the mother. It is important to recognize that it is not the individual meals a pregnant woman eats during pregnancy that might affect development, but the consequence of her exposure history over her life, which has the greatest impact on her body burden. Again, good nutrition, including a diet with appropriate levels of fat, has consequences on dietary intake and consequent body burdens of dioxin and related compounds. Nursing infants represent special cases who, for a limited portion of their lives, may have elevated exposures on a body-weight basis when compared with non-nursing infants and adults (see discussion). In addition to breast milk exposures, intakes of CDD/CDFs and dioxin-like PCBs are more than three times higher for a young child than those of an adult, on a body-weight basis. Table 4-9 in Section 4 of this document describes the variability in average intake values as a function of age using age-specific food consumption rates and average food concentrations, as was done for adult intake estimates. However, as with for the nursing infants, the differences in body burden between children and adults are expected to be much less than the differences in daily intake. Assuming that body burden is the relevant dose metric for most if not all effects, there is some assurance that these increased intake levels will have limited additional impact on risk as compared with overall lifetime exposure.

Background exposures to dioxin and related compounds need to be considered when evaluating both hazard and risk.

The term “background” exposure has been used throughout this reassessment to describe exposure of the general population, who are not exposed to readily identifiable point sources of dioxin-like compounds. Adult daily intakes of CDD/CDFs and dioxin-like PCBs are estimated to

average 45 and 25 pg TEQ_{DFP}-WHO_{98}/day, respectively, for a total intake of 70 pg/day TEQ_{DFP}-WHO_{98}. Daily intake is estimated by combining exposure media concentrations (food, soil, air) with contact rates (ingestion, inhalation). Table 4-8 summarizes the intake rates derived by this method. The intake estimate is supported by an extensive database on food consumption rates and food data. PK modeling provides further support for the intake estimates. Current adult tissue levels reflect intakes from past exposure levels, which are thought to be higher than current levels (see Trends, Section 2.6).

CDD/CDF and dioxin-like PCB intakes for the general population may extend to levels at least three times higher than the mean. Variability in general-population exposure is primarily a result of differences in dietary choices that individuals make. These are differences in both quantity and types of food consumed. A diet that is disproportionately high in animal fats will result in an increased background exposure over the mean. Data on variability of fat consumption indicate that the 95th percentile is about twice the mean and the 99th percentile is approximately three times the mean. Additionally, a diet that substitutes meat sources that are low in dioxin (i.e., beef, pork, or poultry) with sources that are high in dioxin (i.e., freshwater fish) could result in exposures elevated more than three times the mean. This scenario may not represent a significant change in total animal fat consumption, even though it results in an increased dioxin exposure. Intakes of CDD/Fs and dioxin-like PCBs are over three times higher for a young child as compared to that of an adult, on a body weight basis. Using age-specific food consumption rate and average food concentrations, as was done above for adult intake estimates, Table 4-9 describes the variability in average intake values as a function of age.

The average CDD/CDF tissue level for the general adult United States population appears to be declining; the best estimate of current (late 1990s) levels is 25 ppt (TEQ_{DFP}-WHO_{98}, lipid basis). The tissue samples collected in North America in the late 1980s and early 1990s showed an average TEQ_{DFP}-WHO_{98} level of about 55 pg/g lipid. This finding is supported by a number of studies, all conducted in North America, that measured dioxin levels in adipose tissue, blood, and human milk. The number of people in most of these studies, however, is relatively small and the participants were not statistically selected in ways that assured their representativeness of the general United States adult population. One study, the 1987 National Human Adipose Tissue Survey (NHATS), involved more than 800 individuals and provided broad geographic coverage, but did not address coplanar PCBs. Similar tissue levels of these compounds have been measured in Europe and Japan during similar time periods.

Because dioxin levels in the environment have been declining since the 1970s (see trends discussion), it is reasonable to expect that levels in food, human intake, and ultimately human tissue have also declined over this period. The changes in tissue levels are likely to lag the decline seen in environmental levels, and the changes in tissue levels cannot be assumed to occur proportionally with declines in environmental levels. CDC (2000) summarized levels of CDDs,

CDFs, and PCBs in human blood collected during the time period 1995 to 1997. The individuals sampled were all U.S. residents with no known exposures to dioxin other than normal background. The blood was collected in seven different locations from 400 individuals with an age range of 20 to 70 years. All TEQ calculations were made assuming nondetects were equal to half the detection limit. Although these samples were not collected in a manner that can be considered statistically representative of the national population and lack wide geographic coverage, they are judged to provide a better indication of current tissue levels in the United States than the earlier data (see Table 4-7). PCBs 105, 118, and 156 are missing from the blood data for the comparison populations reported in the Calcasieu study (CDC, 2000). These congeners account for 62% of the total PCB TEQ estimated in the early 1990s. Assuming that the missing congeners from the Calcasieu study data contribute the same proportion to the total PCB TEQ as in earlier data, they would increase our estimate of current body burdens by another 3.7 pg TEQ/g lipid for a total PCB TEQ of 5.9 pg/g lipid and a total DFP TEQ of 25 pg/g lipid.

Past background exposure of about 3 pg TEQ/ kgBW/day leads to body burdens in the human population that currently average approximately 5 ng/kg (20-30 pg TEQ/g lipid) when all dioxins, furans and PCBs are included; body burdens have been higher in the past. DeVito et al. (1995) estimated that body burdens averaged 9-13 ng/kg based on intake values of 4-6 pg TEQ/kg/day and blood levels of 40-60 pgTEQ/g lipid using data from the late 1980s. If the general population were exposed to dioxins and related compounds at the current level of intake (approximately 1 pg TEQ/kg/day) for a lifetime, average steady-state body burdens would be <2 ng/kg and blood levels would be 7-8 pg TEQ/g lipid. These estimates are based on the assumption of 50% absorption of dioxin-like compounds from the diet. Using the same assumption used for intake values, high-end estimates of body burden of individuals in the general population (approximately the top 5%) may be more than twice as high as these average estimates. This calculation is based on data for dietary fat consumption and the assumption that body burdens of dioxin and related compounds in the general population are associated with fat consumption. The top 1% is likely to be three times higher based on its intake of fat.

Characterizing national background levels of dioxins in tissues is uncertain because the current data cannot be considered statistically representative of the general population. The task is also complicated by the fact that tissue levels are a function of both age and birth year. Because intake levels have varied over time, the accumulation of dioxins in a person who turned 50 in 1990 is different from that in a person who turned 50 in 2000. Future studies should help address these uncertainties. The National Health and Nutrition Examination Survey (NHANES) began a new national survey in 1999 that will measure dioxin blood levels in about 1,700 people per year (see http:www.cdc.gov/nchs/nhanes.htm). The survey is conducted at 15 different locations per year and is designed to select individuals statistically representative of the civilian U.S. population

in terms of age, race, and ethnicity. These new data should provide a much better basis than the currently available data for estimating national background tissue levels and evaluating trends.

As described above, current intake levels from food sources are estimated in this reassessment to be approximately 1 pg TEQ/KgBW/day. Certain segments of the population may be exposed to additional increments of exposure by being in proximity to point sources or because of dietary practices. These will be described below.

Evaluation of exposure of "special" populations and developmental stages is critical to risk characterization.

As discussed above, background exposures to dioxin-like compounds may extend to levels at least three times higher than the mean. This upper range is assumed to result from the normal variability of diet and human behaviors. Exposures from local elevated sources or unique diets would be in addition to this background variability. Such elevated exposures may occur in small segments of the population, such as individuals living near discrete local sources, or subsistence or recreational fishers. Nursing infants represent a special case where, for a limited portion of their lives, these individuals may have elevated exposures on a body-weight basis when compared to non-nursing infants and adults. This exposure will be discussed in a separate section.

Dioxin contamination incidents involving the commercial food supply have occurred in the United States and other countries. For example, in the United States, contaminated ball clay was used as an anticaking agent in soybean meal and resulted in elevated dioxin levels in some poultry and catfish. This incident involved less than 5% of national poultry production and has since been eliminated. Elevated dioxin levels have also been observed in a few beef and dairy animals where the contamination was associated with contact with pentachlorophenol-treated wood. This kind of elevated exposure was not detected in the national beef survey. Consequently, its occurrence is likely to be low, but it has not been determined. These incidents may have led to small increases in dioxin exposure to the general population. However, it is unlikely that such incidents have led to disproportionate exposures to populations living near where these incidents have occurred, because in the United States meat and dairy products are highly distributed on a national scale. If contamination events were to occur in foods that are predominantly distributed on a local or regional scale, then such events could lead to highly exposed local populations.

Elevated exposures associated with the workplace or industrial accidents have also been documented. United States workers in certain segments of the chemical industry had elevated levels of TCDD exposure, with some tissue measurements in the thousands of ppt TCDD. There is no clear evidence that elevated exposures are currently occurring among United States workers. Documented examples of past exposures for other groups include certain Air Force personnel exposed to Agent Orange during the Vietnam War and people exposed as a result of industrial accidents in Europe and Asia.

Consumption of unusually high amounts of fish, meat, or dairy products containing elevated levels of dioxins and dioxin-like PCBs can lead to elevated exposures in comparison to the general population. Most people eat some fish from multiple sources, both fresh and salt water. The typical dioxin concentrations in these fish and the typical rates of consumption are included in the mean background calculation of exposure. People who consume large quantities of fish at typical contamination levels may have elevated exposures because the concentration of dioxin-like compounds in fish is generally higher than in other animal food products. These kinds of exposures are addressed within the estimates of variability of background and are not considered to result in highly exposed populations. If high-end consumers obtain their fish from areas where the concentration of dioxin-like chemicals is elevated, they may constitute a highly exposed subpopulation. Although this scenario seems reasonable, no supporting data could be found for such a highly exposed subpopulation in the United States. One study measuring dioxin-like compounds in blood of sports fishers in the Great Lakes area showed elevations over mean background, but within the range of normal variability. Elevated CDD/CDF levels in human blood have been measured in Baltic fishermen. Similarly, elevated levels of coplanar PCBs have been measured in the blood of fishers on the north shore of the Gulf of the St. Lawrence River who consume large amounts of seafood.

High exposures to dioxin-like chemicals as a result of consuming meat and dairy products would occur only in situations where individuals consume large quantities of these foods and the level of these compounds is elevated. Most people eat meat and dairy products from multiple sources and, even if large quantities are consumed, they are not likely to have unusually high exposures. Individuals who raise their own livestock for basic subsistence have the potential for higher exposures if local levels of dioxin-like compounds are high. One study in the United States showed elevated levels in chicken eggs near a contaminated soil site. European studies at several sites have shown elevated CDD/CDF levels in milk and other animal products near combustion sources.

In summary, in addition to general population exposure, some individuals or groups of individuals may also be exposed to dioxin-like compounds from discrete sources or pathways locally within their environment. Examples of these “special” exposures include contamination incidents, occupational exposures, direct or indirect exposure to local populations from discrete sources, or exposures to subsistence or recreational fishers.

Breast-feeding infants have higher intakes of dioxin and related compounds for a short but developmentally important part of their lives. However, the benefits of breast feeding are widely recognized to outweigh the risks.

Two studies have compared dioxins in infants who have been breast-fed versus those who have been formula-fed, and both have shown elevations in the concentrations of dioxins in infants

being breast-fed. Formula-fed infants had lipid-based concentrations < 5 ppt TEQ_{DF}-WHO_{98} whereas breast-fed infants had average lipid-based concentrations above 20 ppt TEQ_{DF}-WHO_{98} (maximum of 35 ppt TEQ_{DF}-WHO_{98}). The dose to the infant varies as a function of infant body weight, the concentration of dioxins in the mother's milk, and the trend of dioxins in the mother's milk to decline over time. Doses at birth could exceed 200 pg TEQ_{DFP}-WHO_{98}/kg/day, which would drop to about 20 pg TEQ_{DFP}-WHO_{98}/kg/day after 12 months. The average dose over a year was calculated to be 77 pg TEQ_{DFP}-WHO_{98}/kg/day. Although this average annual infant dose of 77 pg TEQ_{DFP}-WHO_{98}/kg/day exceeds the currently estimated adult dose of 1 pg TEQ_{DFP}-WHO_{98}/kg/day, the effect on infant body burdens is expected to be less dramatic, i.e., infant body burdens will not exceed adult body burdens by 77 times. This is due to the rapidly expanding infant body weight and lipid volume, the decrease in concentration of dioxins in the mother's milk over time, and possibly more rapid elimination in infants. A pharmacokinetic exercise comparing a 12-month nursing scenario with formula feeding showed infant lipid concentrations to exceed 40 ppt TEQ_{DFP}-WHO_{98}, compared with lipid concentrations less than 10 ppt for the formula-fed infants. The dioxin concentrations in these two hypothetical children merged at about 10 years of age, at a lipid concentration of about 13 ppt TEQ_{DFP}-WHO_{98}.

The American Academy of Pediatrics (1997) has made a compelling argument for the diverse advantages of breast-feeding and the use of human milk for infant feeding to infants, mother, families and society. These include health, nutritional, immunologic, developmental, psychological, social, economic, and environmental benefits. Breast milk is the point of comparison for all infant food, and the breast-fed infant is the reference for evaluation of all alternative feeding methods. In addition, increasing the rates of breast-feeding initiation is a national health objective and one of the goals of the United States Government's Healthy People 2010. The World Health Organization (1988) maintained that the evidence did not support an alteration of WHO recommendations that promote and support breast-feeding. A more recent consultation in 1998 (WHO, 2000) reiterated these conclusions. Although it is important that the recommendations of these groups continue to be reevaluated in light of emerging scientific information, the Agency does not believe that finding contained in this report provides a scientific basis for initiating such a reevaluation. This conclusion is based on the fact that stronger data have been presented that body burden, not intake, is the best dose metric; that many of the noncancer effects, particularly those seen in children, are more strongly associated with prenatal exposure and the mother's body burden rather than postnatal exposures and breast milk levels; and that dioxin-like compounds are strong promoters of carcinogenicity, a mode of action that depends on late-stage impacts rather than early-stage impacts on the carcinogenic process.

Many dioxin sources have been identified and emissions to the environment are being reduced.

Current emissions of CDDs/CDFs/PCBs to the United States environment result principally from anthropogenic activities. Evidence that supports this finding includes matches in time of rise of environmental levels with rise in general industrial activity (see trend discussion in Section 4.6), lack of any identified large natural sources and observations of higher CDD/CDF/PCB body burdens in industrialized versus less industrialized countries (see discussion on human tissue levels in Section 4.4).

The principal identified sources of environmental release may be grouped into five major types: (1) combustion and incineration sources; (2) chemical manufacturing/processing sources; (3) industrial/municipal processes; (4) biological and photochemical processes; and (5) reservoir sources. Development of release estimates is difficult because only a few facilities in most industrial sectors have been tested for CDD/CDF emissions. Thus an extrapolation is needed to estimate national emissions. The extrapolation method involves deriving an estimate of emissions per unit of activity at the tested facilities and multiplying this by the total activity level in the untested facilities. In order to convey the level of uncertainty in both the measure of activity and the emission factor, U.S. EPA developed a qualitative confidence rating scheme. The confidence rating scheme, presented in Section 4, Table 4-1, uses qualitative criteria to assign a high, medium, or low confidence rating to the emission factor and activity level for those source categories for which emission estimates can be reliably quantified. The dioxin reassessment has produced an inventory of source releases for the United States (Table 4-2). The inventory was developed by considering all sources identified in the published literature and numerous individual emissions test reports. The inventory is limited to sources whose releases can be reliably quantified (i.e., those with confidence ratings of A, B, or C as defined above). Also, it is limited to sources with releases that are created essentially simultaneously with formation. This means that the reservoir sources are not included. The inventory presents the environmental releases in terms of two reference years: 1987 and 1995. EPA's best estimates of releases of CDD/CDFs to air, water, and land from reasonably quantifiable sources were approximately 2,800 gram (g) (1.3 pounds) TEQ_{DF}-WHO_{98} in 1995 versus 13,500 g (6 pounds) TEQ_{DF}-WHO_{98} in 1987. The decrease in estimated releases of CDD/CDFs between 1987 and 1995 (approximately 80%) was due primarily to reductions in air emissions from municipal and medical waste incinerators.

The environmental releases of CDD/CDFs in the United States occur from a wide variety of sources, but are dominated by releases to the air from combustion sources. Insufficient data are available to comprehensively estimate point-source releases of dioxin-like compounds to water. Sound estimates of releases to water are available only for chlorine-bleached pulp and paper mills and manufacture of ethylene dichloride/vinyl chloride monomer. The contribution of dioxin-like compounds to waterways from nonpoint source reservoirs is likely to be greater than

the contributions from point sources. Current data are only sufficient to support preliminary estimates of nonpoint source contributions of dioxin-like compounds to water (i.e., urban storm water runoff and rural soil erosion). These estimates suggest that, on a nationwide basis, total nonpoint releases are significantly larger than point source releases. Other releases to water bodies that cannot be quantified on the basis of existing data include effluents from POTWs and most industrial/commercial sources.

Based on the available information, the inventory includes only a limited set of activities that result in direct environmental releases to land. The only releases to land quantified in the inventory are land application of sewage sludge and pulp and paper mill wastewater sludges. Not included in the inventory's definition of an environmental release is the disposal of sludges and ash into approved landfills. While this inventory is the most comprehensive and well-documented in the world, it is likely to underestimate total releases. The magnitude of the underestimate is unknown but it is unlikely that noncombustion sources today, other than reservoir sources, play a dominant role in human exposure. In terms of 1995 releases from reasonably quantifiable sources, this document estimates releases of 2,800 g $WHO_{98}TEQ_{DF}$ for contemporary formation sources and 2,900 g $WHO_{98}TEQ_{DF}$ for reservoir sources. In addition, there remain a number of unquantifiable and poorly quantified sources that are described in Section 4.

As described above, combustion appears to be the most significant process of formation of CDDs/CDDFs today. Important factors that can affect the rate of dioxin formation include the overall combustion efficiency, post-combustion flue gas temperatures and residence times, and the availability of surface catalytic sites to support dioxin synthesis. Although chlorine is an essential component for the formation of CDD/CDFs in combustion systems, the empirical evidence indicates that for commercial-scale incinerators, chlorine levels in feed are not the dominant controlling factor for rates of CDD/CDF stack emissions. The conclusion that chlorine in feed is not a strong determinant of dioxin emissions applies to the overall population of commercial scale combustors. For any individual commercial-scale combustor, circumstances may exist in which changes in chlorine content of feed could affect dioxin emissions. For uncontrolled combustion, such as open burning of household waste, chlorine content of wastes may play a more significant role in affecting levels of dioxin emissions than observed in commercial-scale combustors.

No significant release of newly formed dioxin-like PCBs is occurring in the United States. Unlike CDD/CDFs, PCBs were intentionally manufactured in the United States in large quantities from 1929 until production was banned in 1977. Although it has been demonstrated that small quantities of coplanar PCBs can be produced during waste combustion, no strong evidence exists that the dioxin-like PCBs make a significant contribution to TEQ releases during combustion. The occurrences of dioxin-like PCBs in the U.S. environment most likely reflects past releases associated with PCB production, use, and disposal. Further support of this finding is based on observations of reductions since 1980s in PCBs in Great Lakes sediment and other areas.

It is unlikely that the emission rates of CDD/CDFs from known sources correlate proportionally with general population exposures. Although the emissions inventory shows the relative contribution of various sources to total emissions, it cannot be assumed that these sources make the same relative contributions to human exposure. It is quite possible that the major sources of dioxin in food (see discussion in Section 2.6 indicating that the diet is the dominant exposure pathway for humans) may not be those sources that represent the largest fractions of total emissions in the United States. The geographic locations of sources relative to the areas from which much of the beef, pork, milk, and fish come is important to consider. That is, much of the agricultural areas that produce dietary animal fats are not located near or directly downwind of the major sources of dioxin and related compounds.

The contribution of reservoir sources to human exposure may be significant. Several factors support this finding. First, human exposure to the dioxin-like PCBs is thought to be derived almost completely from reservoir sources. Because one-third of general population TEQ exposure is due to PCBs, at least one-third of the overall risk from dioxin-like compounds comes from reservoir sources. Second, CDD/CDF releases from soil via soil erosion and runoff to waterways appear to be greater than releases to water from the primary sources included in the inventory. CDD/CDFs in waterways can bioaccumulate in fish-leading to human exposure via consumption of fish, which makes up about one-third of the total general population CDD/CDF TEQ exposure. This suggests that a significant portion of the CDD/CDF TEQ exposure could be due to releases from the soil reservoir. Finally, soil reservoirs could have vapor and particulate releases that deposit on plants and enter the terrestrial food chain. The magnitude of this contribution, however, is unknown.

This assessment adopts the hypothesis that the primary mechanism by which dioxin-like compounds enter the terrestrial food chain is via atmospheric deposition. Dioxin and related compounds enter the atmosphere directly through air emissions or indirectly, for example, through volatilization from land or water or from resuspension of particles. Once introduced into the environment, dioxin-like compounds are widely distributed in the environment as a result of a number of physical and biological processes. The dioxin-like compounds are essentially insoluble in water, generally classified as semivolatile, and tend to bioaccumulate in animals. Some evidence has shown that these compounds can degrade in the environment, but in general they are considered very persistent and relatively immobile in soils and sediments. These compounds are transported through the atmosphere, as vapors or attached to airborne particulates and can be deposited on soils, plants, or other surfaces (by wet or dry deposition). The dioxin-like compounds enter water bodies primarily via direct deposition from the atmosphere, or by surface runoff and erosion. From soils, these compounds can reenter the atmosphere either as resuspended soil particles or as vapors. In water, they can be resuspended into the water column from sediments, volatilized out of the surface waters into the atmosphere, or become buried in

deeper sediments. Immobile sediments appear to serve as permanent sinks for the dioxin-like compounds. Though not always considered an environmental compartment, these compounds are also found in anthropogenic materials (such as pentachlorophenol) and have the potential to be released from these materials into the broader environment.

The two primary pathways for the dioxin-like compounds to enter the ecological food chains and human diet are air-to-plant-to-animal and water/sediment-to-fish. Vegetation receives these compounds via atmospheric deposition in the vapor and particle phases. The compounds are retained on plant surfaces and bioaccumulated in the fatty tissues of animals that feed on these plants. Vapor-phase transfers onto vegetation have been experimentally shown to dominate the air-to-plant pathway for the dioxin-like compounds, particularly for the lower chlorinated congeners. In the aquatic food chain, dioxins enter water systems via direct discharge or deposition and runoff from watersheds. Fish accumulate these compounds through direct contact with water, suspended particles, and bottom sediments and through the consumption of aquatic organisms. Although these two pathways are thought to normally dominate contribution to the commercial food supply, others can also be important. Elevated dioxin levels in cattle resulting from animal contact with pentacholorophenol-treated wood have been documented by the USDA. Animal feed contamination episodes have led to elevations of dioxins in poultry in the United States, milk in Germany, and meat/dairy products in Belgium.

Deposition can occur directly onto soil or onto plant surfaces. At present, it is unclear whether atmospheric deposition represents primarily current contributions of dioxin and related compounds from all media reaching the atmosphere or whether it is past emissions of dioxin and related compounds which persist and recycle in the environment. Understanding the relationship between these two scenarios will be particularly important in understanding the relative contributions of individual point sources of these compounds to the food chain and assessing the effectiveness of control strategies focused on either current or past emissions of dioxins in attempting to reduce the levels in food.

As discussed in Section 4.3, estimates for background levels of dioxin-like compounds in environmental media are based on a variety of studies conducted at different locations in North America. Of the studies available for this compilation, only those conducted in locations representing “background” were selected. The amount and representativeness of the data varies, but in general these data lack the statistical basis to establish true national means. The environmental media concentrations were consistent among the various studies and were consistent with similar studies in Western Europe. These data are the best available for comparing site-specific values to national background levels. Because of the limited number of locations examined, however, it is not known if these ranges adequately capture the full national variability; if significant regional variability exists, making national means of limited utility; or if elevated levels above this range could still be the result of background contamination processes.

As new data are collected, these ranges are likely to be expanded and refined. The limited data on dioxin-like PCBs in environmental media are summarized in the document (Part I, Volume 3, Chapter 4), but were not judged adequate for estimating background levels.

Concentrations of CDDs/CDFs and PCBs in the United States environment were consistently low prior to the 1930s. Then concentrations rose steadily until about 1970. At this time, the trend reversed and concentrations have declined to the present. The most compelling supportive evidence of this trend for CDD/CDFs and PCBs comes from dated sediment core studies. Sediment concentrations in these studies are generally assumed to be an indicator of the rate of atmospheric deposition. CDD/CDF and PCB concentrations in sediments began to increase around the 1930s and continued to increase until about 1970. Decreases began in 1970 and have continued to the time of the most recent sediment samples (about 1990). Sediment data from 20 United States lakes and rivers from seven separate research efforts consistently support this trend. Additionally, sediment studies in lakes located in several European countries have shown similar trends.

It is reasonable to assume that sediment core trends should be driven by a similar trend in emissions to the environment. The period of increase generally matches the time when a variety of industrial activities began rising, and the period of decline appears to correspond with growth in pollution abatement. Many of these abatement efforts should have resulted in decreases in dioxin emissions, i.e., elimination of most open burning, particulate controls on combustors, phaseout of leaded gas, and bans on PCBs, 2,4,5-T, hexachlorophene, and restrictions on use of pentachlorophenol. Also, the national source inventory of this assessment documented a significant decline in emissions from the late 1980s to the mid-1990s. Further evidence of a decline in CDD/CDF levels in recent years is emerging from data, primarily from Europe, showing declines in foods and human tissues.

In addition to the congener-specific PCB data discussed earlier, a wealth of data on total PCBs and Aroclor mixtures exist that also supports these trends. It is reasonable to assume that the trends for dioxin-like PCBs are similar to those for PCBs as a class because the predominant source of dioxin-like PCBs is the general production of PCBs in Aroclor mixtures. PCBs were intentionally manufactured in large quantities from 1929 until production was banned in the United States in 1977. United States production peaked in 1970, with a volume of 39,000 metric tons. Further support is derived from data showing declining levels of total PCBs in Great Lakes sediments and biota during the 1970s and 1980s. These studies indicate, however, that during the 1990s the decline slowed and may be leveling off.

Because dioxin-like chemicals are persistent and accumulate in biological tissues, particularly in animals, the major route of human exposure is through ingestion of foods containing minute quantities (part per trillion or ppt levels) of dioxin-like compounds. This results

in widespread low-level exposure of the general population to dioxin-like compounds. The issue of general population background exposure was discussed earlier.

Risk Characterization Summary Statement

Based on all of the data reviewed in this reassessment and scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the potential to produce a spectrum of effects. Some of these effects may be occurring in humans at general population background levels and may be resulting in adverse impacts on human health. The potency and fundamental level at which these compounds act on biological systems is analogous to several well-studied hormones. Dioxin and related compounds have the ability to alter the pattern of growth and differentiation of a number of cellular targets by initiating a series of iochemical and biological events, resulting in the potential for a spectrum of cancer and noncancer responses in animals and humans. Despite this potential, there is currently no clear indication of increased disease in the general population attributable to dioxin-like compounds. The lack of a clear indication of disease in the general population should not be considered strong evidence for no effect of exposure to dioxin-like compounds. Rather, lack of a clear indication of disease may be a result of the inability of current data and scientific tools to directly detect effects at these levels of human exposure. Several factors suggest a need to further evaluate the impact of these chemicals on humans at or near current background levels. These are the weight of the evidence on exposure and effects, an apparently low margin of exposure for noncancer effects, potential for significant risks to some portion of the general population, and additivity to background processes related to carcinogenicity in the case of incremental exposures above background.

Table 1-1. The TEF scheme for I-TEQ$_{DF}$ [a]

Dioxin (D) congener	TEF	Furan (F) congener	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
1,2,3,4,6,7,8,9-OCDD	0.001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		1,2,3,4,6,7,8,9-OCDF	0.001

[a]Note that the scheme does not include dioxin-like PCBs. The nomenclature for this scheme is I-TEQ$_{DF}$, where 'I' represents "International," TEQ represents the 2,3,7,8-TCDD toxic equivalence of the mixture, and the subscript DF indicates that only dioxins (Ds) and furans (Fs) are included in the TEF scheme.

Table 1-2. The TEF scheme for TEQ_{DFP}-WHO_{94}[a]

Dioxin (D) congener	TEF	Furan (F) congener	TEF	Dioxin-like PCB (P)	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1	PCB-77	0.0005
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.05	PCB-126	0.1
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5	PCB-169	0.01
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1	PCB-105	0.0001
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1	PCB-118	0.0001
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1	PCB-123	0.0001
1,2,3,4,6,7,8,9-OCDD	0.001	2,3,4,6,7,8-HxCDF	0.1	PCB-156	0.0005
		1,2,3,4,6,7,8-HpCDF	0.01	PCB-157	0.0005
		1,2,3,4,7,8,9-HpCDF	0.01	PCB-167	0.00001
		1,2,3,4,,6,7,8,9-OCDF	0.001	PCB-114	0.0005
				PCB-170	0.0001
				PCB-180	0.00001
				PCB-189	0.0001

[a]The nomenclature for this TEF scheme is TEQ_{DFP}-WHO_{94}, where TEQ represents the 2,3,7,8-TCDD toxic equivalence of the mixture, and the subscript DFP indicates that dioxins (Ds), furans (Fs), and dioxin-like PCBs (P) are included in the TEF scheme. The subscript 94 following WHO displays the year changes were made to the TEF scheme.

Table 1-3. The TEF scheme for TEQ_{DFP}-WHO_{98}[a]

Dioxin (D) congener	TEF	Furan (F) congener	TEF	Dioxin-like PCB (P)	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1	PCB-77	0.0001
1,2,3,7,8-PeCDD	1.0	1,2,3,7,8-PeCDF	0.05	PCB-81	0.0001
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5	PCB-126	0.1
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1	PCB-169	0.01
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1	PCB-105	0.0001
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1	PCB-118	0.0001
1,2,3,4,6,7,8,9-OCDD	0.000 1	2,3,4,6,7,8-HxCDF	0.1	PCB-123	0.0001
		1,2,3,4,6,7,8-HpCDF	0.01	PCB-156	0.0005
		1,2,3,4,7,8,9-HpCDF	0.01	PCB-157	0.0005
		1,2,3,4,6,7,8,9-OCDF	0.0001	PCB-167	0.00001
				PCB-114	0.0005
				PCB-189	0.0001

[a]The nomenclature for this TEF scheme is TEQ_{DFP}-WHO_{98}, where TEQ represents the 2,3,7,8-TCDD toxic equivalence of the mixture, and the subscript DFP indicates that dioxins (Ds), furans (Fs), and dioxin-like PCBs (P) are included in the TEF scheme. The subscript 98 following WHO displays the year changes were made to the TEF scheme. Note that the changes to the TEFs since 1994 are as follows:

- For 1,2,3,7,8-PeCDD, the new WHO TEF is 1 and the I-TEF is 0.5;
- For OCDD, the new WHO TEF is 0.0001 and the I-TEF is 0.001;
- For OCDF, the new WHO TEF is 0.0001 and the I-TEF is 0.001;
- For PCB 77, the new TEF is 0.0001;
- The addition of PCB 81 (i.e., 3,4,4',5-TCB); and
- For the two di-ortho substituted HpCBs in the 1994 TEF scheme (i.e., PCBs 170 and 180), no TEFs have been assigned in the new WHO TEF scheme.

Table 2-1. Effects of TCDD and related compounds in different animal species

Effect	Human	Monkey	Guinea Pig	Rat	Mouse	Hamster	Cow	Rabbit	Chicken	Fish	Avian wildlife	Marine mammals	Mink
Presence of AhR	+	+	0	+	+	+	+	+	+	+	+	+	+
Binding of TCDD: AhR Complex to the DRE (enhancer)	+		+	+	+	+	+	+	+	+			
Enzyme induction	+	+	+	+	+	+		+	+	+	+	+	+
Acute lethality	0	+	+	+	+	+	+	+	+	+	+	+	+
Wasting syndrome		+	+	+	+	+	+	+		+	+	+	+
Teratogenesis/fetal toxicity, mortality	+/-	+	+	+	+	+		+	+	+	+	+	+
Endocrine effects	+/-	+		+	+					+	+	+	+
Immunotoxicity	+/-	+	+	+	+	+	+		+	+		+	
Carcinogenicity	+/-			+	+	+				+			
Neurotoxicity	+	+		+	+				+				
Chloracnegenic effects	+	+			+		+	+		+			
Porphyria	+	0	0	+	+	0			+				
Hepatotoxicity	+	+	+/-	+	+	+/-	+	+	+	+	+	+	+
Edema		+	0	0	+	+			+	+			
Testicular atrophy		+	+	+	+								
Bone marrow hypoplasia		+	+		+/-				+				

+ = observed.
+/- = observed to limited extent, or +/- results.
0 = not observed.
Blank cells = no data.

Table 3-1. Early molecular events in response to dioxin

Diffusion into the cell
Binding to the AhR protein
Dissociation from hsp90
Active translocation from cytoplasm to nucleus
Association with Arnt protein
Conversion of liganded receptor to the DNA-binding form
Binding of liganded receptor heteromer to enhancer DNA
Enhancer activation
Altered DNA configuration
Histone modification
Recruitment of additional proteins
Nucleosome disruption
Increased accessibility of transcriptional promoter
Binding of transcription factors to promoter
Enhanced mRNA and protein synthesis

These events are discussed in detail in Part II, Chapter 2.

Table 4-1. Confidence rating scheme

Confidence category	Confidence rating	Activity level estimate	Emission factor estimate
Categories/media for which emissions can be reasonably quantified			
A	High	Derived from comprehensive survey	Derived from comprehensive survey
B	Medium	Based on estimates of average plant activity level and number of plants or limited survey	Derived from testing at a limited but reasonable number of facilities believed to be representative of source category
C	Low	Based on data judged possibly nonrepresentative.	Derived from testing at only a few, possibly nonrepresentative facilities or from similar source categories
Categories/media for which emissions cannot be reasonably quantified			
D	Preliminary Estimate	Based on extremely limited data, judged to be clearly nonrepresentative.	Based on extremely limited data, judged to be clearly nonrepresentative.
E	Not Quantified	No data.	1) Argument based on theory but no data 2) Data indicating dioxin formation, but not in a form that allows developing an emission factor

Table 4-2. Quantitative inventory of environmental releases of TEQ_{DF}-WHO_{98} in the United States

Emission source category	Confidence rating[a] Reference year 1995			Confidence rating[a] Reference year 1987		
	A	B	C	A	B	C
Releases (g TEQ_{DF}-WHO_{98} /yr) to Air						
Waste Incineration						
Municipal waste incineration		1250			8877	
Hazardous waste incineration		5.8			5	
Boilers/industrial furnaces			0.39			0.78
Medical waste/pathological incineration			488			2590
Crematoria			9.1			5.5
Sewage sludge incineration		14.8			6.1	
Tire combustion			0.11			0.11
Pulp and paper mill sludge incinerators[f]						
Power/Energy Generation						
Vehicle fuel combustion - leaded[b]			2			37.5
- unleaded			5.9			3.6
- diesel			35.5			27.8
Wood combustion - residential			62.8			89.6
- industrial		27.6			26.4	
Coal combustion - utility		60.1			50.8	
Oil combustion - industrial/utility			10.7			17.8
Other High Temperature Sources						
Cement kilns (hazardous waste burning)			156.1			117.8
Lightweight aggregate kilns burning hazardous waste			3.3			2.4
Cement kilns (nonhazardous waste burning)			17.8			13.7
Petroleum refining catalyst regeneration			2.21			2.24
Cigarette combustion			0.8			1
Carbon reactivation furnaces			0.08			0.06
Kraft recovery boilers		2.3			2	
Minimally Controlled or Uncontrolled Combustion						
Forest, brush, and straw fires[d]			208			170
Metallurgical Processes						
Ferrous metal smelting/refining						
- Sintering plants		28				32.7
Nonferrous metal smelting/refining						
- Primary copper		<0.5[e]			<0.5[e]	
- Secondary aluminum			29.1			16.3
- Secondary copper			271			983
- Secondary lead		1.72			1.29	
Drum and barrel reclamation			0.08			0.08
Chemical Manufac./Processing Sources						
Ethylene dichloride/vinyl chloride		11.2				
Total quantified releases to air[c]	2705			13081		

Table 4-2. Quantitative inventory of environmental releases of TEQ_{DF}-WHO_{98} in the United States (continued)

Emission source category	Confidence rating[a] Reference year 1995			Confidence rating[a] Reference year 1987		
	A	B	C	A	B	C
Releases (g TEQ/yr) to water						
Chemical Manuf./Processing Sources Bleached chemical wood pulp and paper mills	19.5			356		
Ethylene dichloride/vinyl chloride		0.43				
Total quantified releases to water[c]	19.93			356		
Releases (g TEQ/yr) to land						
Chemical Manuf./Processing Sources Bleached chemical wood pulp and paper mill sludge	1.4			14.1		
Ethlyene dichloride/vinyl chloride		0.73				
Municipal wastewater treatment sludge	76.6			76.6		
Commercially marketed sewage sludge	2.6			2.6		
2,4-Dichlorophenoxy acetic acid	28.9			33.4		
Total quantified releases to land[c]	110.23			126.7		
Overall quantified releases to the open and circulating environment	2835			13564		

Confidence Rating A = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **High Confidence** in the **Emission Factor** and **High Confidence** in **Activity Level**.
Confidence Rating B = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Medium Confidence** in the **Emission Factor** and at least **Medium Confidence** in **Activity Level**.
Confidence Rating C = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Low Confidence** in either the Emission Factor and/or the **Activity Level**.

[a]A confidence rating reflects EPA's judgment as to the adequacy of information pertaining to the emission factor and activity level.
[b]Leaded fuel production and the manufacture of motor vehicle engines requiring leaded fuel for highway use have been prohibited in the United States. (see Section 4.1 for details.)
[c]TOTAL reflects only the total of the estimates made in this report.
[d]It is not known what fraction, if any, of the estimated emissions from forest fires represents a "reservoir" source. The estimated emissions may be solely the result of combustion.
[e]Congener-specific emissions data were not available; the I-TEQ_{DF} emission estimate was used as a surrogate for the TEQ_{DF}-WHO_{98} emission estimate.
[f]Included within estimate for Wood Combustion - Industrial.

Table 4-3. Preliminary indication of the potential magnitude of TEQ_{DF}-WHO_{98} releases from "unquantified" (i.e., Category D) sources in reference year 1995

Emission source category	Release medium	Preliminary release estimate (g WHO_{98}-TEQ_{DF}/yr)
I. Contemporary Formation Sources Biogas Combustion	Air	0.22[a]
Oil Combustion-Residential	Air	6.0[a]
Coal Combustion - Commercial/Industrial	Air	39.6[a]
Coal Combustion - Residential	Air	32.0[a]
Asphalt Mixing Plants	Air	7[a]
Combustion of Landfill Gas	Air	6.6
Landfill Fires	Air	1,050[a]
Accidental Fires (Structural)	Air	>20[a]
Accidental Fires (Vehicles)	Air	28.3[a]
Backyard Barrel Burning	Air	804
Coke Production	Air	6.9[a]
Electric Arc Ferrous Furnaces	Air	44.3[a]
Ferrous Foundries	Air	17.5[a]
Municipal Wastewater	Water	12
II. Reservoir Sources Urban Runoff	Water	190[a]
Rural Soil Erosion	Water	2,700[a]

[a]Congener-specific emissions data were not available; the I-TEQ_{DF} emission factor was used as a surrogate for the TEQ_{DF}-WHO_{98} emissions estimate.

Table 4-4. Unquantified sources

Category	Unquantified sources
Combustion sources	Uncontrolled combustion of PCBs Agricultural burning
Metal smelting and refining	Primary aluminum Primary magnesium Primary nickel
Chemical manufacturing	Mono- to tetrachlorophenols Pentachlorophenol Chlorobenzenes Chlorobiphenyls (leaks/spills) Dioxazine dyes and pigments 2,4-Dichlorophenoxy acetic acid Tall oil-based liquid soaps
Biological and photochemical processes	Composting
Reservoir sources	Air Sediments Water Biota PCP-treated wood

Table 4-5. Estimates of the range of typical background levels of dioxin-like compounds in various environmental media

Media	TEQ_{DF}-WHO_{98} concentrations
Rural soils	1-6 pg/g (ppt)
Urban soils	7-20 pg/g
Sediments	1-60 pg/g
Rural air	0.002-0.02 pg/m^3
Urban air	0.02-0.2 pg/m^3

Table 4-6. Estimates of levels of dioxin-like compounds in food

Food type	CDD/CDFs (pg TEQ_{DF}-WHO_{98}/g fresh weight)	PCBs (pg TEQ_{P}-WHO_{98}/g fresh weight)	Total (pg TEQ_{DFP}-WHO_{98}/g fresh weight)
Beef	0.2	0.094	0.29
Pork	0.22	0.09	0.31
Eggs	0.032	0.1	0.13
Chicken	0.11	0.044	0.15
Milk	0.031	0.016	0.047
Dairy products	0.12	0.058	0.18
Marine fish	0.36	0.25	0.61
Freshwater fish	1.2	1.2	2.4
Marine shellfish	0.79	0.042	0.83
Vegetable fats	0.056	0.037	0.093
Water	0.00056 (pg/L)	NA	NA

NA = not available.

Table 4-7. Background serum levels in the United States 1995 - 1997

	TEQ_{DFP} WHO_{98} (pg/g lipid)	2,3,7,8-TCDD (pg/g lipid)
Median	18.7	1.9
Mean	22.1*	2.1
95th Percentile	38.8	4.2

* After adjusting to account for missing PCBs, the mean is 25.4 pg/g lipid.

Source: CDC, 2000.

Table 4-8. Adult contact rates and background intakes of dioxin-like compounds

Exposure route	Contact rate	Dioxins and furans		Dioxin-like PCBS		Total intake (pg TEQ_{DFP}-WHO_{98}/kg-d)
		Concentration TEQ_{DF}-WHO_{98}	Intake (pg TEQ_{DF}-WHO_{98}/kg-d)	Concentration TEQ_{P}-WHO_{98}	Intake (pg TEQ_{P}-WHO_{98}/kg-d)	
Soil ingestion	50 mg/d	12 pg/g	0.0085	NA	NA	0.0085
Freshwater fish	6 g/d	1.2 pg/g	0.13	1.2 pg/g	0.11	0.24
Marine fish	12.5 g/d	0.36 pg/g	0.064	0.25 pg/g	0.045	0.11
Marine shellfish	1.6 g/d	0.79 pg/g	0.018	0.042 pg/g	0.0096	0.028
Inhalation	13.3 m^3/d	0.12 pg/m^3	0.023	NA	NA	0.023
Milk	175 g/d	0.031 pg/g	0.078	0.016 pg/g	0.040	0.12
Dairy	55 g/d	0.12 pg/g	0.094	0.058 pg/g	0.046	0.14
Eggs	0.24 g/kg-d	0.032 pg/g	0.0077	0.10 pg/g	0.024	0.032
Beef	0.67 g/kg-d	0.20 pg/g	0.13	0.094 pg/g	0.063	0.19
Pork	0.22 g/kg-d	0.22 pg/g	0.048	0.009 pg/g	0.0020	0.05
Poultry	0.49 g/kg-d	0.11 pg/g	0.054	0.044 pg/g	0.022	0.076
Vegetable fat	17 g/d	0.056 pg/g	0.014	0.037 pg/g	0.0090	0.023
Water	1.4 L/d	0.0005 pg/L	0.000011	NA	NA	0.000011
Total			**0.65 (45 pg/d)**		**0.35 (25 pg/d)**	**1.0 (70 pg/d)**

Table 4-9. Variability in average daily TEQ intake as a function of age

Age range	Intake, mass basis pg TEQ_{DFP}-WHO_{98}/d	Intake, body weight basis pg TEQ_{DFP}-WHO_{98}/kg-d
1-5 yr	54	3.6
6-11 yr	58	1.9
12-19 yr	63	1.1
Adult	70	1

Table 5-1. Serum dioxin levels in the background population and epidemiological cohorts (back-calculated)

Cohort	No.	Total TEQ ppt lipid			2,3,7,8-TCDD ppt lipid	PCBs	Non-2,3,7,8-TCDD TEQ ppt lipid	Comment
		Lower	Central Tend.	Upper	Central Tendency	Mean TEQ	Central Tendency	
CDC comparison population, USA 1995 - 97; CDC 2000	316	2[a]	25.4 mean[b]	50[a]	2.1 mean 1.9 median (95% UCL = 4.2)	5.3 (est.)[b]	23.3 mean	TEQ_{DFP}-WHO_{98}; serum; missing PCBs 105, 118, 156 estimated
Background, Dioxin Assessment, USA ~1990s	pooled results	30	52.8 mean 55 median	70	5.2 mean SD ~1.32[c]	18.8 mean 20 median	47.6 mean	TEQ_{DFP}-WHO_{98}; serum, adipose, breast milk[d]
Back-Calculated								
Ranch Hand, low; Ketchum et al. 1999	276				52.3 median (range 27 - 94)			serum
Ranch Hand, high; Ketchum et al. 1999	283				195.7 median (range 94 - 3,290)			serum
Hamburg cohort women; Flesch-Janys et al. 1999	$65_{2,3,7,8}$ 64_{TEQ}	19.3[e]	811.2 mean[e] 172.8[5] median	6789.1[e]	506.8 mean 125.8 median (range 2.4 - 6397.4)		304.4 mean[e]	I-TEQs, dioxin and furan TEQ only; serum
NIOSH, Fingerhut et al. 1991b, NTIS	253				2,000 mean (range[f] 2 - 32,000)			serum
BASF, severe chloracne; Ott et al. 1993	56				1008 geom. mean (range[g] 20 - 13360)			serum
BASF, moderate chloracne; Ott et al. 1993	59				420.8 geom. mean (range[g] 2.72 - 4915)			serum
BASF, no chloracne; Ott et al. 1993	139				38.4 geom. mean (range[g] 2.72 - 2981)			serum
Seveso Zone A; Landi et al. 1998	7				230 geom. mean 325.9 median (range 41.2 - 399.7)			serum
Seveso Zone A, medical; Needham et al. 1999	296				381 - 489 median (range 1.5 - 56,000)			Samples taken 1976, not back-calculated; serum; using ½ DL

Table 5-1. Serum dioxin levels in the background population and epidemiological cohorts (back-calculated) (continued)

Seveso Zone B; Landi et al. 1998	51				47.5 geom. mean 52.5 median (range 5.3 - 273)			serum
Seveso Zone B, medical; Needham et al. 1999	80				87 - 147 median (range 1.8 - 725)			Samples taken 1976, not back-calculated; serum; using ½ DL
Seveso Zone R, medical; Needham et al. 1999	48				15 - 89 median (range 1 - 545)			Samples taken 1976; not back-calculated; serum; using ½ DL
Seveso NonABR; Landi et al. 1998	52				4.9 geom. mean 5.5 median (range 1.0 - 18.1)			serum
Dutch Accident; Hooiveld et al. 1996	14				1841.8 arith. mean 1433.8 geom. mean (range 301 - 3683)			serum
Dutch Main Production; Hooiveld et al. 1996	5				608.2 arith. mean 285.9 geom. mean (range 17 - 1160)			serum

[a] Estimated from ATSDR 1999 Calcasieu comparison population graph.
[b] CDC data scaled upward to adjust for missing data on PCB congeners 105, 118 and 156, by matching to PCB congener ratios measured in the early 1990s.
[c] SD approximated from unweighted estimate.
[d] Weighted average levels for the subset of serum lipid TEQs were 4.54 ng/kg for 2,3,7,8-TCDD, and 55.4 ng/kg for total TEQ (PCB contribution not adjusted for missing congeners).
[e] PCDD and PCDF derived TEQ only, using I-TEFs.
[f] Lower interval on current level.
[g] Range estimated from exponential log distribution graph.

Table 5-2. Doses yielding 1% excess risk (95% lower confidence bound) based upon 2-year animal carcinogenicity studies using simple multistage (Portier et. al, 1984) models[a]

Tumor	Shape	ED_{01}	
		Animal intake for 1% excess risk in ng/kg/day (95% lower confidence bound)	Steady-state body burden in ng/kg at ED_{01} (95% lower confidence bound)
Liver cancer in female rats (Kociba)	Linear	0.77 (0.57)	14 (10)
Squamous cell carcinoma of the tongue in male rats (Kociba)	Linear	14.1 (5.9)	254 (106)
Squamous cell carcinoma of the nasal turbinates or hard palate in male rats (Kociba)	Cubic	41.4 (1.2)	746 (22)
Squamous cell carcinoma of the lung in female rats (Kociba)	Cubic	40.4 (2.7)	730 (48)
Squamous cell carcinoma of the nasal turbinates or hard palate in female rats (Kociba)	Linear	5.0 (2.0)	90 (36)
Thyroid follicular cell adenoma in male rats (NTP)	Linear	4.0 (2.1)	144 (76)
Thyroid follicular cell adenoma in female rats (NTP)	Cubic	33.0 (3.1)	1,190 (112)
Liver adenomas and carcinomas in female rats (NTP)	Quadratic	13.0 (1.7)	469 (61)
Liver adenomas and carcinomas in male mice (NTP)	Linear	1.3 (0.86)	20.6 (13.6)
Liver adenomas and carcinomas in female mice (NTP)	Linear	15.1 (7.8)	239 (124)
Thyroid follicular cell adenomas and carcinomas in female mice (NTP)	Linear	30.1 (14.0)	478 (222)
Subcutaneous tissue sarcomas in female mice (NTP)	Lin-Cubic	43.2 (14.1)	686 (224)
Leukemias and lymphomas in female mice (NTP)	Linear	10.0 (5.4)	159 (86)

[a] Reprinted with slight modifications from Chapter 8, Table 8.3.2.

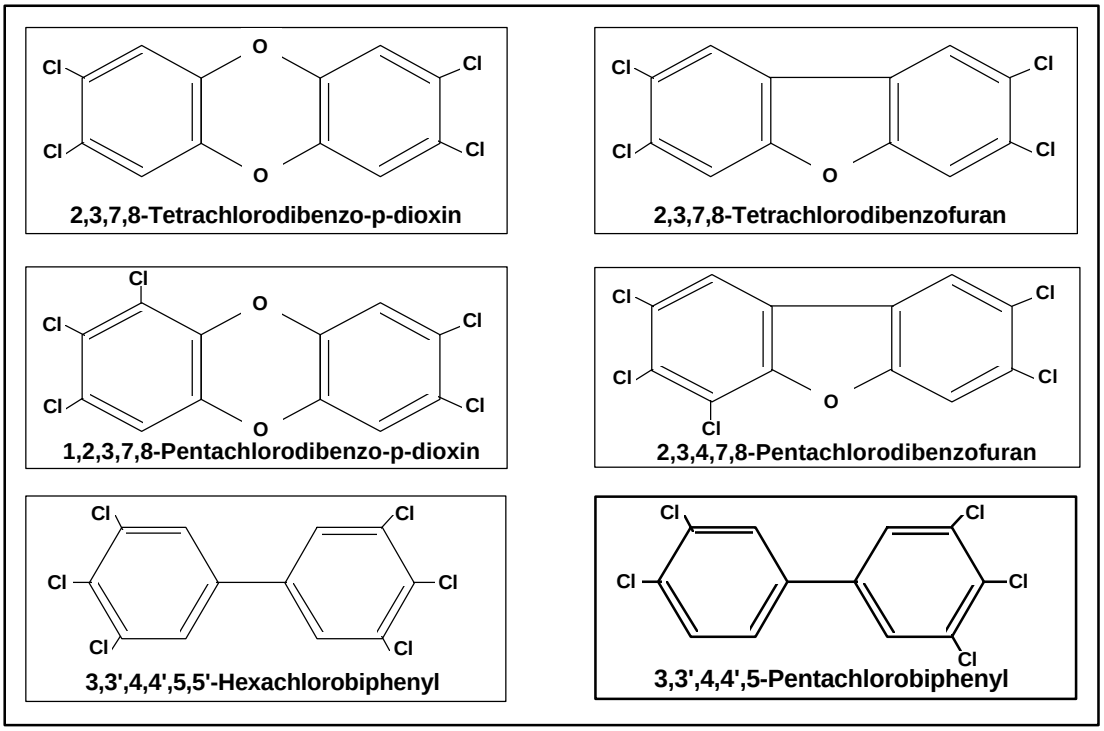


Figure 1-1. Chemical structure of 2,3,7,8-TCDD and related compounds.

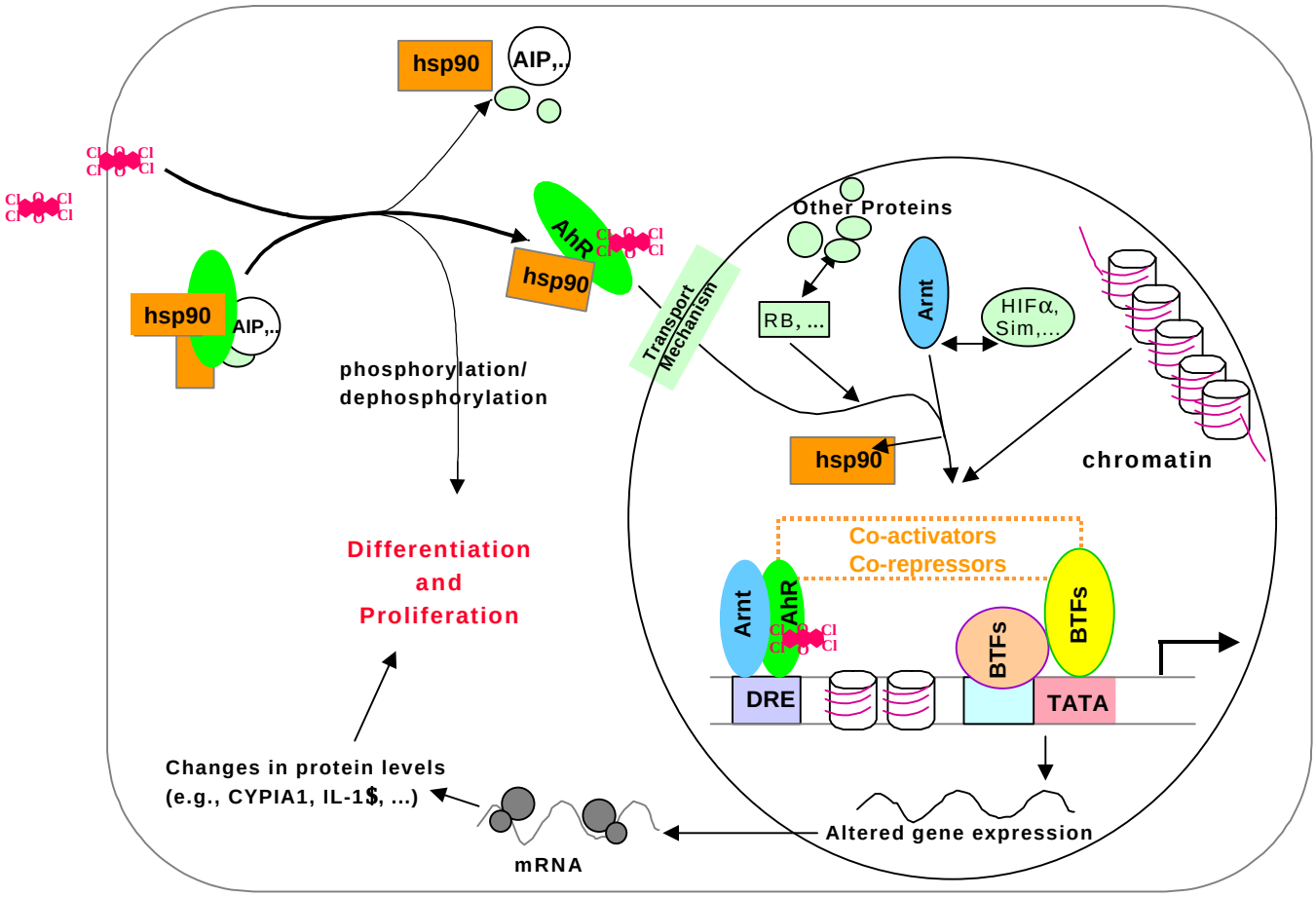
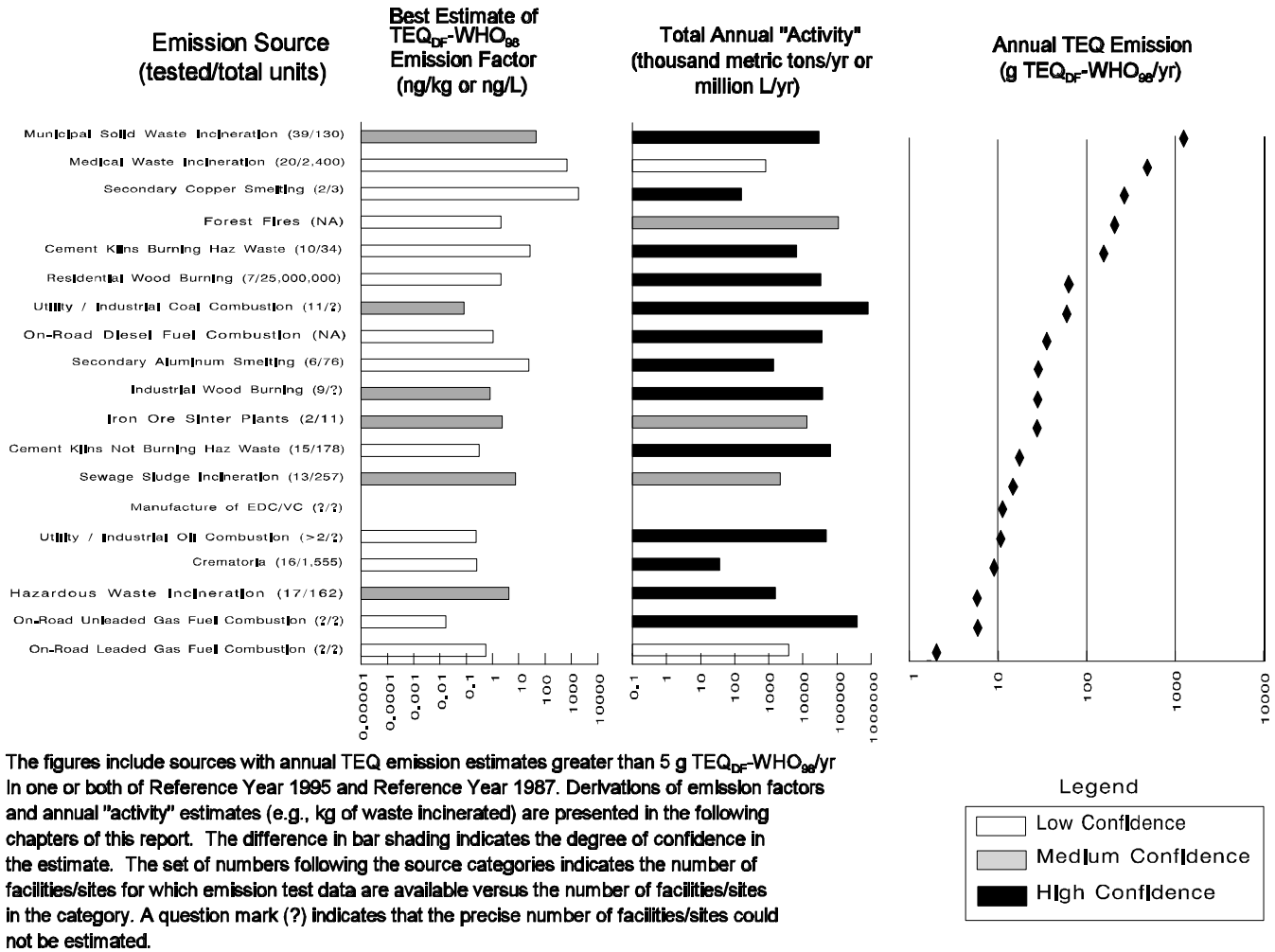


Figure 2-1. Cellular mechanism for AhR action.
TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; AhR, aryl hydrocarbon receptor; AIP, associated immunophilin-like protein; hsp90, 90 kilodalton heat shock protein; p, sites of phosphorylization; Arnt, AhR nuclear translocator protein; RB, retinoblastoma protein; NF-kB, nuclear transcription factor; HIF, hypoxia inducible factor; DRE, dioxin-responsive element; BTFs, basal transcription factors; TATA, DNA recognition sequence.

CYP1A1	TGF-α
CYP1A2	TGF-β
CYP1B1	Plasminogen Activator Inhibitor-2
Glutathione S-Transferase Ya	Interleukin-1β
Aldehyde-3-Dehydrogenase	c-*fos*
NAD(P)H:Quinone Oxidoreductase	jun

Figure 2-2. Some of the genes whose expression is altered by exposure to TCDD.



The figures include sources with annual TEQ emission estimates greater than 5 g TEQ_{DF}-WHO_{98}/yr in one or both of Reference Year 1995 and Reference Year 1987. Derivations of emission factors and annual "activity" estimates (e.g., kg of waste incinerated) are presented in the following chapters of this report. The difference in bar shading indicates the degree of confidence in the estimate. The set of numbers following the source categories indicates the number of facilities/sites for which emission test data are available versus the number of facilities/sites in the category. A question mark (?) indicates that the precise number of facilities/sites could not be estimated.

Figure 4-1. Estimated CDD/CDF I-TEQ emissions to air from combustion sources in the United States, 1995.

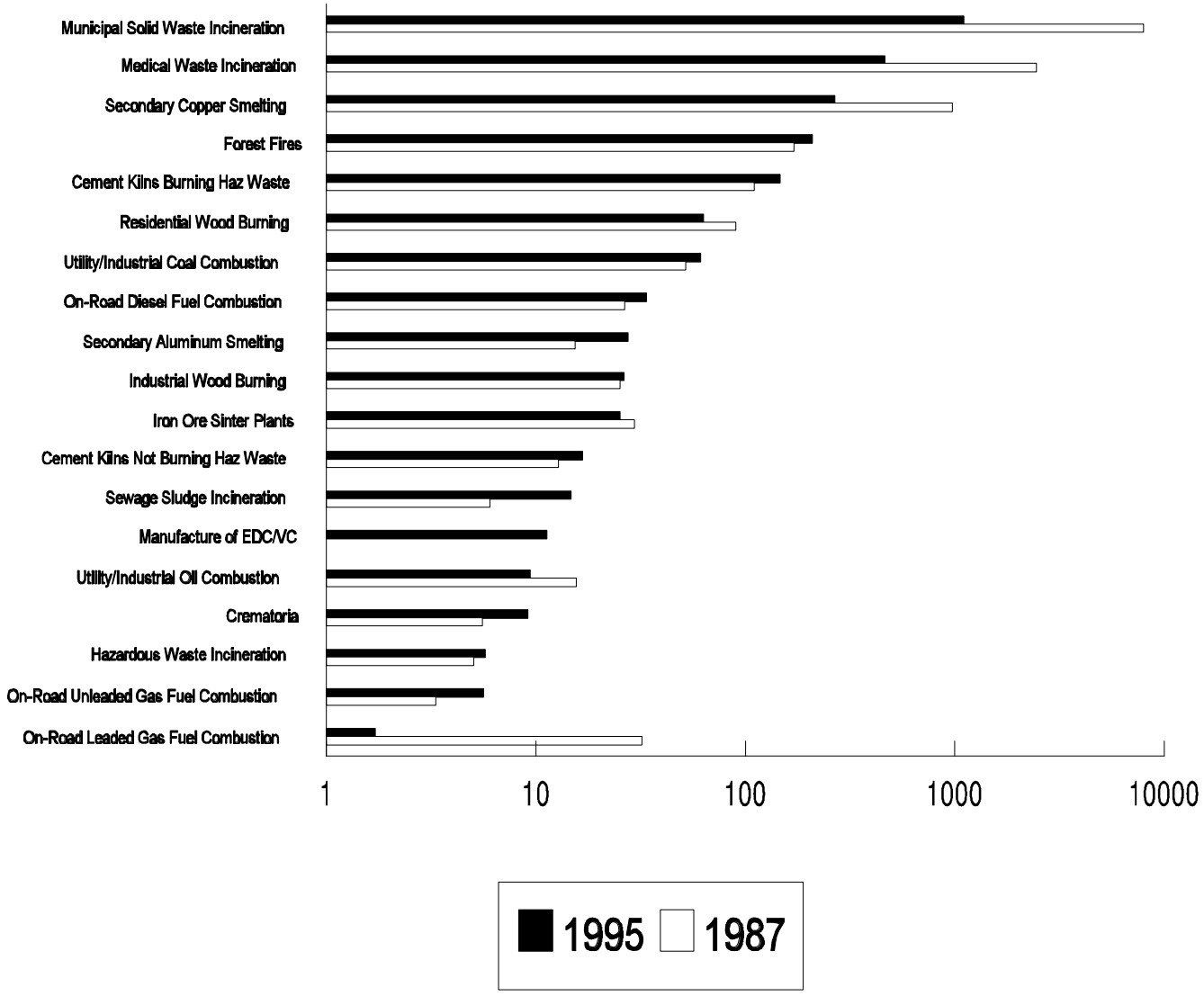


Figure 4-2. Comparison of estimates of annual I-TEQ emissions to air (grams I-TEQ/yr) for reference years 1987 and 1995.

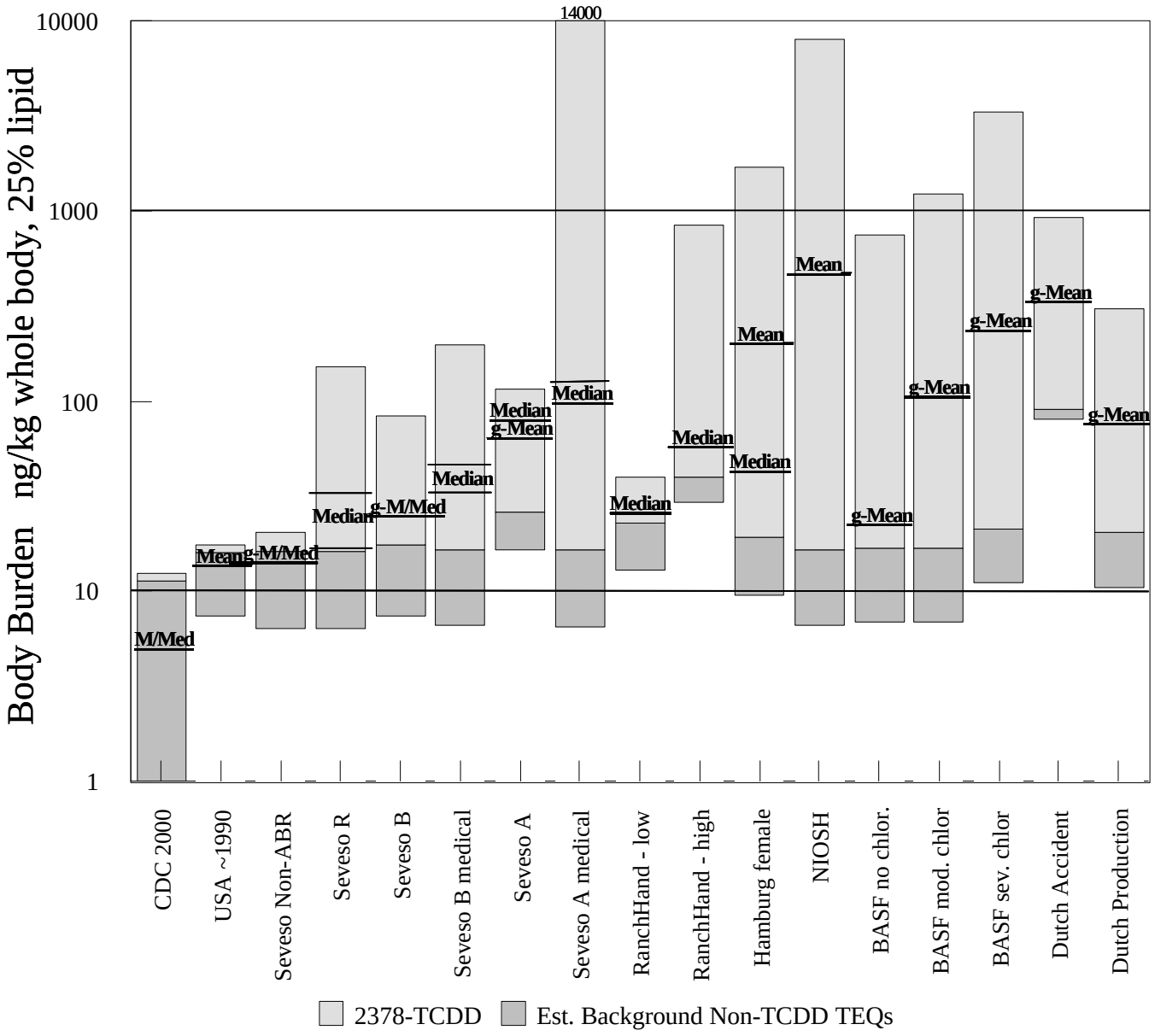


Figure 5-1. Dioxin body burden levels in background populations and epidemiological cohorts (back-calculated).

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